

**PATENT COOPERATION TREATY**  
**PCT**  
**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**  
**(PCT Article 36 and Rule 70)**

Applicant's or agent's file reference <b>WO 525</b>	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. <b>PCT/EP 03/50287</b>	International filing date (day/month/year) <b>07.07.2003</b>	Priority date (day/month/year) <b>08.07.2002</b>
International Patent Classification (IPC) or both national classification and IPC <b>C07K14/47</b>		
Applicant <b>APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
- This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.
3. This report contains indications relating to the following items:
- I  Basis of the opinion
  - II  Priority
  - III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV  Lack of unity of invention
  - V  Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI  Certain documents cited
  - VII  Certain defects in the international application
  - VIII  Certain observations on the international application

Date of submission of the demand <b>02.02.2004</b>	Date of completion of this report <b>06.10.2004</b>
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer <b>Groenendijk, M</b> Telephone No. +31 70 340-3715



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50287

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

### Description, Pages

1-26 as originally filed

### Claims, Numbers

1-19 as originally filed

### Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP 03/50287

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-19
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-19
Industrial applicability (IA)	Yes: Claims	1-19
	No: Claims	

2. Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/50287

**Re Item V**

Reasoned statement under Art.35 PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1:WO-A-0134631

D2:Weinstein, "Chemistry and biochemistry of amino acids, peptides and proteins",  
1983, 267-357

D3:WO-A-0107473

**I.Novelty**

In view of the available prior art the present claims 1-19 are considered to be novel under Art.33(2) PCT.

**II.Inventive step**

1)For the present subject-matter D1 is considered to be the closest prior art, disclosing the  $\beta$ - sheet breaking peptide LPFFD having one or more modifications and/or substitutions, particularly N- and C-terminal modifications, changes of side-chains, alpha-carbon substitutions, changes of chirality, cyclization and amide bond modifications. The effect of said modifications is improved pharmacological properties, particularly increasing the enzymatic stability while maintaining or increasing the activity, brain uptake and solubility (e.g., see page 7, line 6 to page 8, line 9).

2)The present compounds differ from said prior art compounds therein that they comprise one or more N-alpha-alkylations. The effect of said modification is improved pharmacological properties, particularly increasing the enzymatic stability while maintaining or increasing the activity, brain uptake and solubility.

3)However it was well-known in the prior art that N-alpha-alkylation improves enzymatic stability without being detrimental to the activity, as can be illustrated by D2 (see especially pages 278-281, 284-292 and 338-345) and D3 (e.g., page 6, lines 7-22), which moreover indicates that said substitutions also reduce the tendency to aggregation into extended  $\beta$ -sheets.

It is therefore considered that a skilled person would have a fair expectation that introduction of an N-alpha-alkyl group in the peptide according to formula I of claim 1 would increase the enzymatic stability while maintaining, at least qualitatively, the activity.

Therefore, In order to acknowledge inventive step for said compounds they should

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/50287

exhibit unexpected advantageous properties compared with those disclosed in D1. However no such properties have been posed or have become plausible otherwise. Therefore the claims 1-14 and the related claims 15-19 are considered to lack inventive step under Art.33(3) PCT.